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10/049,373	06/21/2002	Isao Ishida	051023-0115	3667

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,373	ISHIDA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-25* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,9 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record is now Thaian N. Ton of Art Unit 1632.

Applicants' Response and Amendment, filed 11/30/04, has been considered and entered. Claim 7 has been cancelled. Claims 6 and 10-24 are withdrawn. Claim 25 has been added. Claims 1-5 and 8-9 have been amended. Claims 1-6, 8-25 are pending. Claims 1-5, 8, 9, and 25 are under current examination.

Election/Restrictions

Claims 6 and 10-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/4/04.

Information Disclosure Statement

Applicants' IDS, filed 6/21/02 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8, 9, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 1-5, 8 and 9 have been amended such that the amendment introduces new matter to the disclosure. The claims now recite a trans-chromosomic non-human mammal (see claim 1, and its dependent claims) or a cell from a transchromosomic nonhuman mammal (see claim 9). This is considered new matter because there is no support in the specification for the term "trans-chromosomic non-human mammal". Applicants point to p. 77 (Example 5) for support for "trans-chromosomic". Example 5 provides literal support for a trans-chromosomic mouse, but there is no specific recitation of a trans-chromosomic non-human mammal. The term "trans-chromosomic" is not specifically described by the instant specification, it broadly encompasses mammals that have an extra chromosome, or animals which have an extra sequence from a human chromosome. The specification fails to provide adequate description for this term, and thus, the claimed invention as whole is not adequately described if the claims require essential or critical elements which are not adequately described by the specification.

The addition of claim 25 constitutes new matter because the claim encompasses both promoters endogenous to the human cytochrome p450 gene and other promoters that would induce the expression of the gene. There is no description provided by the instant specification which teaches the breadth of these embodiments. The specification fails to provide adequate description for the claim, and thus, the claimed invention as whole is not adequately described if the claims require essential or critical elements which are not adequately described by the specification.

Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient, relevant identifying characteristics (as it relates to the invention as a whole), such that one of skill in the art would recognize that Applicants had possession of the claimed invention.

MPEP § 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP § 2163.02 teaches that, "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the

application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP § 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure."

The prior rejection of claims 1-5 and 9 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims, as instantly amended, are directed to a trans-chromosomic nonhuman mammal comprising a cell which harbors a human chromosome fragment expressing at least one human cytochrome P450 gene (claims 1-5) and a cell or tissue from the mammal (claim 9).

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now*

claimed." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Applicants argue that in the prior Office action, the Examiner believed the invention to be that of a transgenic mouse, of which the resulting phenotype is highly unpredictable, but that Applicants argue that because the present human chromosome fragment is not integrated into the genome, one can reliably predict a phenotype. See p. 7, part (ii) of the Response. Further, Applicants argue that the present application details 26 working examples that teach a variety of experimental techniques for making the claimed non-human mammal. For examples, Applicants point to introduction of a human chromosome fragment into an ES cell via microcell fusion in order to produce a chimeric animal, and thus, Applicants conclude that the disclosed methods are sufficiently descriptive that one of skill could predictably transform a cell from a mammal other than a mouse and mouse cells, that are exemplified in the examples. See p. 7, last ¶ of the Response. Applicants argue that because no DNA is integrated into the cell's genome of the non-human mammal, the reasons for rejection in the prior Office action do not apply. Applicants argue that the cited art of record is directed to transgenic animals, not the animals as instantly claimed, wherein the trans-chromosomic fragment is not integrated into the host cell's genome. Thus, Applicants argue that the skilled artisan would understand that any phenotype exhibited by the host cell

genome is due to the introduction of the chromosomal fragment, and not due to a disruption of the native genetic material. See p. 8 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. The claims, as currently amended, broadly encompass both animals which are transgenic (*i.e.*, where a transgene, which has a human chromosome fragment is integrated into the genome) and animals which have an extra chromosome. There is no limitation in the claims which recites that the human chromosome fragment is or is not part of the genome of the mammal. As such, the cited art of record and prior arguments presented in the previous Office action are considered germane to the instant rejection. In particular, that there is no description of the phenotype of any mammal, other than a mouse, and that a particular phenotype(s) of the claimed mammals cannot be reasonably predicted in light of the art. See prior Office action, page 4, and Wood and Hammer, recited therein. Furthermore, it has been previously determined that, in light of the instant disclosure, that a representative number of species have not been sufficiently descr8ibed by other relevant identifying characteristics. This is clear given the limited information disclosed in the specification, and that an artisan would not have been able to predict whether the mammals encompassed by the breadth of the claims, would have the same or different phenotypes, when compared to the transgenic mouse. As such, absent sufficient description for the claimed

mammals, the cells derived from those mammals also fail to be sufficiently described.

See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

The prior rejection of claims 1-5, 8, 9, and newly added claim 25 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a trans-chromosomic mouse whose genome comprises a human CYP3A4 gene, wherein administration of a substrate of the CYP3A4 gene-encoded enzyme results in the expression of CYP3A4 enzyme, does not reasonably provide enablement for any non-human trans-chromosomic mammal comprising a cell which harbors a human chromosome fragment expressing at least one human cytochrome P450 gene. The prior rejection is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants argue that because the claimed invention is not integrated into the host chromosomal DNA, and that the chromosomal fragment exists independently of the host genetic material, the basis of the prior rejection (i.e., the unpredictabilities and major consequences of introduction of foreign DNA into host DNA) do not apply. See p. 9 of the Response.

This is not found to be persuasive. Firstly, as stated previously, the breadth of the claims encompasses both animals which are transgenic (*i.e.*, where a transgene, which has a human chromosome fragment is integrated into the genome) and animals which have an extra chromosome. There is no limitation in the claims which recites that the human chromosome fragment is or is not part of the genome of the mammal. As such, the cited art of record and prior arguments presented in the previous Office action are considered germane to the instant rejection. For example, the specification fails to provide guidance on the production of any other

non-human mammal, other than the exemplified mouse. The specification fails to provide guidance as to how to make and use the claimed non-human transchromosomic mammals. The working example of the specification teaches the introduction of a human normal fibroblast-derived chromosome 7 into a mouse ES cell and then by microcell methods, produced a cell line harboring the fragment, and then, by use of an ES cell, produced a chimeric mouse harboring the fragment. See p. 8, lines 15-20. The state of the art of transgenesis, is unpredictable (as evidenced in the prior cited art of record) because the introduction of a particular transgene does not elicit a predictable phenotype. See Hammer *et al.*, p. 7 of the prior Office action. This is pertinent to the claims of record, not only with regard to a transgenic animal, wherein the transgene is integrated into its genome, but a transgenic animal that carries an extra chromosome. There is no teaching or guidance provided by the specification to overcome the unpredictability in this art, for example, that specific cellular factors from different species might not function and produce the same resulting phenotype. The specification does not provide guidance as to the promoter utilized in the claimed invention. The breadth of the claims encompasses using promoters that are endogenous or exogenous. There is no evidence of record that these promoters would be functional in other animals, other than the exemplified mouse, and even if the promoter were active, whether the level of expression of the transgene (i.e., CYP3A4) would be sufficient to produce a certain phenotype.

Applicants provide Kuroiwa as evidence that microcell-mediated chromosome transfer is successful, as evidenced by the production of trans-chromosomic calves that produce human immunoglobulin. See p. 10 1st ¶ of the Response.

Kuroiwa has been considered, but not found to be persuasive. Kuroiwa produced the transchromosomic calves by methods of nuclear transfer, and in particular, the introduction of a fetal bovine fibroblast into an enucleated oocytes. The instant specification fails to support methods of nuclear transfer, careful review of the specification does not reveal any contemplation of production of non-human mammals by methods of nuclear transfer. Furthermore, the art of nuclear transfer is considered unpredictable, with regard to the particular donor cell, and oocytes used. For example, Oback (**Cloning & Stem Cells**, 4(2):147-168 (2002)), who review the state of the art for donor cells used in cloning and state, "Currently, we do not know what makes a good donor cell. In mammals, more than 200 distinct cell types are plainly distinguishable by morphology and more will probably be discovered when better molecular markers become available. Less than 5% of these have been tested as nuclear donors, and they all support development to blastocysts; however, many repeatedly failed to generate viable offspring." See p. 147, 2nd column, 1st ¶. Oback further supports the lack of teachings provided in the art with regard to donor cells that predictably result in live offspring by showing that in different animal species, different somatic donor cells have been tested with varying results. For example, Wakayama and Yanagimachi tested eight cell types in NT

methodology in mice, and found that live offspring were obtained from fibroblast, undefined fetal gonadal and cumulus cells. Further, Kato tested somatic donor cells in cattle and found that all supported development to blastocysts but live offspring were obtained from cumulus, oviduct, skin and liver cells. See pp. 155-156 of Oback. Further, Oback teaches that deciding which cell to use as a donor cell in NT methods is not clear because the cells that have worked in certain species are not the same cells that work in other species, and that they are often dissimilar in their cell cycle stage and their cloning competence. Oback provide a summary of cloning efficiencies from various somatic donor cells (see Table 1). It is noted that different cell types provide different cloning efficiencies with regard to different animal species. Thus, it is clear that the state of the art of nuclear transfer, with regard to different animal species, is unpredictable.

Furthermore, as Applicants have indicated, and the breadth of the claims support, that the non-human mammal comprising a cell which harbors a chromosome fragment expressing at least one human cytochrome p450 gene, encompasses chimeric mammals. However, the specification fails to provide sufficient guidance or teachings with regard to how to use the claimed animals. For example, the claims encompass mammal, wherein one cell has the chromosome fragment. There is no teaching or guidance of record with regard to how many cells which would have to have the fragment in order to practice the claimed invention. Furthermore, there is no teaching or guidance to show how many cells, and how

much expression from those cells, would be sufficient to produce the effect of the expression of the CYP3A4 enzyme upon administration of the enzyme's substrate.

Accordingly, in view of the breadth of the claims, the lack of guidance or teachings provided by the specification, as well as the unpredictability in the art, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The prior rejection of claim 7, under 35 §112, 2nd paragraph, is rendered moot in view of Applicants' cancellation of the claim.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8, 9 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are considered indefinite because they all recite the term "trans-chromosomic". The metes and bounds of this term are unclear. The term trans-chromosomic is not specifically defined in the specification, with regard to a non-human mammal. Furthermore, this term encompasses mammals which have a transgene incorporated into their genome, mammals who carry an extra

chromosome, and chimeric animals which have an extra chromosome in an unspecified number of cells in their body. Appropriate correction/amendment is requested.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8, 9 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Li *et al.* (Archives of Biochem) or Li et al. (Biochem Biophys Res Comm) for reasons of record.

Li teach transgenic mice expressing the human cytochrome p450 CYP3A7 gene, wherein the tissues of the mice express the enzyme, and the enzyme is also activated in an Ames test. The art also teaches backcrossing of the founder mice with the parental strain.

Applicants present the same arguments for both pieces of art. Applicants argue that Li says nothing about a cell that harbors a human chromosomal fragment outside of the host's cellular genome, and thus, cannot anticipate the claimed invention.

This is not persuasive. The claims, as broadly written, encompass the mice, as taught by Li, because Li's mice have cells that have a human chromosome fragment expressing at least one human cytochrome P450 gene. In particular, the transgene that the mice express would be considered a human chromosome

fragment. With regard to Applicants' arguments that Li does not teach a fragment outside of the host's cellular genome, Applicants are arguing limitations that are not found in the claims. There is no recitation of whether the chromosome fragment exists within the mammal's genome or not. As previously, claim 3, which recites particular limitations as to how the mammal is produced fails to have patentable weight, as the claim is directed to the mammal.

Accordingly, it is maintained that Li anticipate the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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